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88. (NEW) The method of claim 76, wherein the administration of the enriched or purified intimin protein is via ingestion, gavage, or intranasal inoculation.

89. (NEW) The method of claim 60, wherein the administration of the enriched or purified intimin protein further comprises at least one adjuvant.

90. (NEW) The method of claim 76, wherein the administration of the enriched or purified intimin protein further comprises at least one adjuvant.

#### REMARKS

Claim 60 has been amended, claims 64 and 65 have been deleted, and claims 66-90 have been added. Therefore, claims 60 and 66-90 are currently pending. Claims 66-75, 83, 87, and 89 are dependent claims which ultimately depend upon independent claim 60, and therefore are subject to all of the limitations of the independent claim. Claim 76 is a new independent claim claiming methods of providing an animal with protection from enterohemorrhagic *E. coli* infection according to the method of claim 60, and dependent claims 77-82, 84-86, 88, and 90 depend from claim 76. As detailed below, these amendments introduce no new matter, and Applicants respectfully request their entry.

Applicants wish to thank Examiner Portner for granting Applicants' representatives, Allen Jensen and Laural Boone, the courtesy of an interview conducted on May 15, 2001. As noted in the interview summary (Paper No. 29), Applicants' representatives discussed the recent publication/presentation by Dr. O'Brien and coworkers at the scientific meeting in Kyoto, Japan. This abstract is discussed in detail below in conjunction with the art rejections.

Claim 60 has been amended to more accurately reflect one embodiment of Applicants' invention. Support for amended claim 60 occurs in the specification as filed at page 14, lines 8-9, which describes providing passive immune protection by administration of anti-intimin antibodies. One embodiment of the instant invention, delineated at page 50, lines 1-7, describes

injecting histidine tagged intimin into a cow's udder, and immunizing the calf by allowing the calf to drink the cow's milk. Support for "enriched or purified intimin" is found in the specification as filed, and specifically in claims 4 and 5 as originally filed. The specification and claims describe both intimin and histidine tagged intimin, and also describe that the histidine tag may be removed. Specification at pages 14-15. The specification also notes that "polyclonal antibodies can be generated from intimin and portions of intimin that are not his-tagged. . . ." Specification at page 58, lines 15-16.

In this amendment, Applicants have added new claims 66-90. Although supported in the application as filed, these claims were not submitted in previous amendments due to the extensive nature of the instant application's prosecution. Over the course of several years, the instant application has been subject to a number of amendments and restriction requirements and was refiled as a continuation application. In order to ease the Examiner's analysis, and to simplify the examination of the claims, Applicants had focused on independent claims until such time as allowable subject matter had been agreed upon. Each of the proposed new claims has support in the claims as originally filed and/or in the specification, or is an inherent feature of the described invention to one of ordinary skill in the art. Entry of these claims, therefore, will not require an additional search and will not raise any issue of new matter. Specifically, the new claims have support in the claims and specification as originally filed as follows:

New Claim	Description	Support
66	domesticated, wildlife, laboratory animal	page 18-19, bridging, lines 1-2
67	cow, rabbit, pig, goat, or mouse	Example IX, page 58 et seq.
68	pregnant or nursing animal	page 46, final paragraph; page 50, lines 1-7
69	offspring of pregnant or nursing animal	page 50, lines 1-7
70	animal, newborn	pages 45-47

New Claim	Description	Support
71	administering via milk, colostrum	page 50, lines 1-7
72	butchering of animal/patient	see discussion below
73	butchering of host animal	see discussion below
74	administering directly to offspring	page 50, lines 1-7
75	birthing then butchering offspring	page 50, lines 1-7; see discussion below
76 (Indep.)	method of providing animal w/ protection from EHEC	same as claims 60, 66
77	cow, rabbit, pig, goat, or mouse	Examples
78	butchering said animal	see discussion below
79	breeding said animal	see discussion below
80	pregnant or nursing animal	page 46, final paragraph; page 50, lines 1-7
81	animal is a cow or calf	page 50, lines 1-7
82	butchering said cow or calf	see discussion below
83	administration via injection	page 48, lines 10-15
84	types of injection	page 48, lines 11-12
85	administration via injection	page 48, lines 10-15
86	types of injection	page 48, lines 11-12
87	administration via ingestion, gavage, or intranasal inoculation	page 48, lines 13-14
88	administration via ingestion, gavage, or intranasal inoculation	page 48, lines 13-14
89	administration w/ adjuvant	Example IX, page 58 et seq.
90	administration w/ adjuvant	Example IX, page 58 et seq.

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In particular, Applicants note that although the term "butchering" as used with respect to the animal patient is not specifically used in the specification, this process is an accepted and expected feature of the cow/veal breeding process (as noted in the specification at page 2, lines 16-19, "[w]ith the prevalence of EHEC in cattle and the subjective nature of differentiating between cooked and undercooked hamburger, a convenient stop at a fast food restaurant, or even a family barbecue, can result in family tragedy."). Likewise, administration to pregnant animals would be understood by one of ordinary skill as within the scope of the disclosed invention as part of the cow/veal/hamburger continuum. As the courts have noted, the specification need not be a blueprint for each and every step, because the specification is not intended to be a production document, and need not describe that which is well-known in the art. *In re Gay*, 309 F.2d 769, 774, 135 U.S.P.Q. 311, 316 (C.C.P.A. 1962); *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q. 1331, 1332 (Fed. Cir. 1991). Therefore, Applicants submit that these claims raise no issue of new matter, and Applicants respectfully request their entry.

Rejection Under 35 U.S.C. §102(b)

The Office rejected claim 60 as allegedly lacking novelty in view of Cravioto et al., *J. Inf. Diseases* 163:1247-1255 (1991). As discussed during the interview with Examiner Portner, Cravioto et al. fails to teach generating anti-intimin antibodies through the administration of enriched or purified intimin protein to a host as claimed in claim 60 as amended. Further, while Cravioto et al. screens colostrum and breast milk for immunoglobulins which would inhibit adherence of EPEC, the colostrum and breast milk came from women who had been infected with the pathogenic bacterium. In fact, Cravioto et al.'s methods require an infection with pathogenic bacteria, and would thus not be useful for methods of preventing infection. Applicants' invention is far superior to the methods presented by Cravioto et al., because the instant invention does not require infection with dangerous bacteria.

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Therefore, in view of the amendments and remarks, Cravioto et al. fail to anticipate Applicants' claimed invention as now claimed, and Applicants respectfully request reconsideration of the rejection and timely allowance of the claims.

Rejection Under 35 U.S.C. §103

The Office rejected claim 60 as allegedly obvious in view of Dougan et al., U.S. Patent No. 5,747,293. Although Applicants continue to traverse this rejection, Applicants also recognize that questions of obviousness are often questions of degree, and address the Office's *prima facie* position as follows.

First, Applicants note that even at this stage of development, the instant invention has found commercial success by being the subject of a license to another commercial entity. This licensee, Biosynexus Inc., has licensed the instant invention from the assignee merely on the strength of the disclosure of the instant application and the underlying research, and prior to allowance of the claims. Therefore, this commercial success is of necessity within the scope of the claimed invention. In view of the early licensing of this technology, this success additionally shows a direct nexus with the invention as disclosed, and is not a result of marketing or other nonscientific factors.

Dean-Nystrom Abstract

As noted in the interview, Dean-Nystrom, Gansheroff, Twiddy, Moon, and O'Brien co-authored an abstract titled "Passive Protection of Suckling Piglets from *Escherichia coli* O157:H7 Infection by Vaccination of Pregnant Sows with Intimin<sub>O157</sub>." This abstract was presented in poster format at the Fourth International Shiga-Toxin Producing *E. coli* Meeting in October 2000 in Kyoto, Japan. The abstract, which is not prior art to the instant application, is attached as Appendix B, and is also listed on the enclosed PTO Form 1449.

In this work, pregnant sows with serum anti-intimin antibody titers of  $\geq 100$  were vaccinated twice with purified intimin protein. This vaccination of the host sows resulted in

colostral anti-intimin titers of  $\geq 100,000$ . The neonatal piglets (i.e., the 'patients') were allowed to suckle for up to eight hours and were then challenged with Shiga-toxin negative EHEC O157:H7. As noted in the abstract, "Most (25/27) piglets nursing the non-vaccinated sow had attaching and effacing (A/E) O157<sup>+</sup> bacteria in the large intestine and  $\geq 10^6$  CFU of inoculum bacteria/g of cecal tissue. In contrast, only 5 of 22 piglets suckling the vaccinated sow had A/E bacteria or  $\geq 10^6$  CFU/g." This experiment confirmed the efficacy of the use of intimin in a passive immunity model system, as proposed by the inventors at the time of filing. (*See also* O'Brien et al., "Intimin: Candidate for an *Escherichia coli* O157:H7 Anti-Transmission Vaccine," Abstract from the Thirty-Second Joint Conference on Cholera and Related Diarrheal Diseases, Nagasaki, Japan, November 14-16, 1996, submitted with the Information Disclosure Statement and PTO Form 1449 dated November 20, 1997.)

The data presented in this abstract show actual results providing passive immune protection which protected patients from an actual challenge with EHEC bacteria. In contrast, Dougan et al. merely states that their antibodies "will therefore be useful in both the detection and/or treatment of EPEC infection" in a patent which focuses on detection methods. Dougan et al., col. 2, lines 41-43. Further, Applicants note again that Dougan et al. noted that "unlike Inv [invasin], which by itself can convert an *E. coli* K12 strain to an organism capable of attaching and invading mammalian cells, Int [intimin] requires the cooperation of other EPEC proteins to induce the effacement and attachment lesion." Dougan et al., col. 2, lines 13-17. *See also* Applicant's Amendment dated March 1, 1999, at page 7. Therefore, Applicants submit that the claimed invention is both novel and nonobvious in view of Dougan et al.

### Conclusion

Applicants respectfully request reconsideration of the rejections and the timely allowance of the pending claims.

Please grant any additional extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Date: May 24, 2001

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APPENDIX A  
VERSION OF CLAIM 60 WITH MARKINGS ACCORDING TO THE AMENDMENT  
OF MAY 24, 2001

60. (Twice Amended) A method for providing passive immune protection to a patient in need thereof comprising:  
generating anti-intimin antibodies through administration of enriched or purified intimin protein to a host; and  
administering an amount of [isolated] the generated anti-intimin antibodies from said host to the patient effective to provide passive immune protection to [a] the patient [in need thereof,];  
wherein the anti-intimin antibodies block binding of enterohemorrhagic *E. coli* to a mammalian cell.

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